

Conferences and Reviews

Current Issues Concerning the Epidemiology of Acquired Immunodeficiency Syndrome and Human Immunodeficiency Virus

Discussant

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This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

HOMER A. BOUSHEY, MD*: *Speculations about the spread of the acquired immunodeficiency syndrome (AIDS) into the general population cause widespread anxiety. Correcting these speculations and focusing concern on the appropriate settings require careful study of the epidemiology of human immunodeficiency virus (HIV) infection. Alan Lifson, MD, MPH, herein reviews what is known about the risks of HIV transmission and the development of AIDS. Dr Lifson's own work has been an important source of information, for his study of serum obtained from homosexual men participating in a trial of hepatitis B vaccine provided early important data on the cumulative risk of AIDS after HIV seroconversion. Dr Lifson has continued to work actively in studying HIV transmission and progression and will summarize some of his observations.*

National and International Epidemiology of AIDS and HIV Infection

ALAN R. LIFSON, MD, MPH†: Ten years ago, reports were published of homosexual men with two then uncommon illnesses: Kaposi's sarcoma and *Pneumocystis carinii* pneumonia.¹ As of August 1, 1991, a total of 186,895 cases of AIDS have been reported to the Centers for Disease Control, including 3,199 cases in children.² According to one estimate, by the end of 1993, a cumulative total of 390,000 to 480,000 cases of AIDS will occur, with 285,000 to 340,000 deaths.³ In 1993 alone, between 61,000 and 98,000 cases of AIDS are expected to occur.

In addition to those men, women, and children with AIDS, many more persons are infected with HIV. The United States Public Health Service has estimated that in mid-1989, about 1 million people in this country were infected with HIV, with at least 40,000 new infections occurring each year among adults and adolescents.³

Cases of AIDS have been reported from every state in the country, with the greatest number from California, Texas,

Florida, New York and New Jersey.² In San Francisco alone, as of August 1, 1991, a total of 10,837 cases of AIDS were reported, with 7,599 deaths; 163 cases and 165 deaths were reported during the month of July alone, representing more than 5 new cases and 5 deaths per day.⁴ According to one projection, between 12,349 and 17,022 cumulative cases of AIDS will be diagnosed in San Francisco through June 1993.⁵

National surveillance data reinforce the fact that AIDS is a disease with a significant effect on young people; for example, 68% of all patients with AIDS are younger than 40 years.² In 1987, 11% of all deaths among men aged 25 to 44 were due to HIV-related causes, compared with less than 1% in 1980; data concerning other causes of mortality suggest that the proportion of HIV-related deaths for 1987 may have been even higher.⁶

Two populations in which AIDS and HIV infection are becoming increasingly evident are women and racial and ethnic minorities. Nationally, 11% of all cases occur in females; this proportion has been increasing over time. For example, from 1989 to 1990, reported cases of AIDS increased by 33% in women, compared with 22% in men.⁷ According to one estimate, if current mortality trends continue, HIV infection or AIDS can be expected to become one of the five leading causes of death in women of reproductive age.⁸

The acquired immunodeficiency syndrome has also had a heavy effect on racial and ethnic minorities. For example, of adults with AIDS, approximately 28% are African American and 16% are Hispanic.² According to 1980 census data, however, about 12% of the population is African American and 6% is Hispanic; therefore, racial and ethnic minorities make up a disproportionately large share of the AIDS cases.⁹ In children, the effect on minorities is even greater; of the children with AIDS, 78% are African American or Hispanic.² From 1989 to 1990, reported cases of AIDS increased by 28% in African Americans and 26% in Hispanics, compared with 20% in whites.⁷

It is also important to emphasize that AIDS is a worldwide epidemic of increasing proportions. Because of under-reporting and underdiagnosis, many more cases of AIDS

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
 HIV = human immunodeficiency virus
 IV = intravenous
 WHO = World Health Organization

have occurred than are reported. According to an estimate from the World Health Organization (WHO), as of December 1990 the actual cumulative global total number of AIDS cases was more than 1.3 million, with about 400,000 cases in children; the greatest number of cases in both adults and children were from sub-Saharan Africa.¹⁰ It is also estimated that between 8 and 10 million persons worldwide may be infected with HIV, with the highest rates of HIV infection again being in sub-Saharan Africa.¹⁰

Although in this review I will primarily focus on AIDS and HIV type 1, it should be noted that HIV-2 has also been reported from a number of areas, particularly in West Africa, and that this virus may also be associated with immunodeficiency and associated diseases.

Patterns of Transmission for HIV

Of adults with AIDS in the US, 59% are homosexual or bisexual men; 7% are homosexual or bisexual men who also report the intravenous (IV) use of drugs; 22% are women or heterosexual men who report the IV use of drugs; 1% are persons with hemophilia or other coagulation disorders; 2% are recipients of blood, blood components, or tissue; 6% are thought to have acquired infection through heterosexual intercourse; and for 4% the risk history is undetermined.² Among those persons thought to have been infected through heterosexual intercourse, 22% are from countries termed pattern II countries by the World Health Organization—including some countries in sub-Saharan Africa or the Caribbean—where most cases of AIDS are presumed due to heterosexual transmission.² The remaining cases are in persons who report heterosexual contact with a partner who is known to be HIV infected or a partner who is a member of a high-risk group.

Although homosexual and bisexual men still account for most AIDS cases, in recent years there has been an increase in the proportion of cases attributed to either heterosexual IV drug use or heterosexual contact. For example, between 1989 and 1990, reported cases of AIDS increased by 19% in homosexual or bisexual men, 24% in female or heterosexual male drug injectors, and (excluding those persons from pattern II countries) 40% in heterosexual contact cases.⁷

The distribution of risk factors can vary greatly in different areas. For example, in San Francisco, 95% of adults with AIDS are homosexual or bisexual men; this includes 9% of adults with AIDS who are homosexual or bisexual men who also report a history of injecting drugs.⁴ In northeastern cities such as New York, the proportion of cases among heterosexual IV drug users is much higher.

Studies of AIDS patients whose risk history is undetermined suggest several major reasons for having "no identified risk."¹¹ Many of these are persons on whom no risk information is available; for example, they may have died or been lost to follow-up before a detailed risk evaluation could be done. Others may have refused to discuss their risk history or denied a history of high-risk sexual or drug use habits to the interviewer for personal, social, or other reasons. Fi-

nally, a person may have been infected through heterosexual contact, but if it was not known for certain that their sexual partner was HIV infected or a member of a high-risk group, they would be classified in the "risk history undetermined" category.

In this country, as well as for much of North America and Europe, most cases of AIDS occur in homosexual or bisexual men or drug injectors. In other countries—including many countries in sub-Saharan Africa—most AIDS cases are thought to have occurred as a result of heterosexual transmission. Patterns of transmission may be changing in many parts of the world. For example, in Central and South America, heterosexual transmission as a risk factor is becoming increasingly apparent.¹² In parts of Asia, where HIV was generally introduced later in the epidemic and fewer cases of AIDS have been reported to date, HIV infection has emerged in a number of populations, such as IV drug users and female prostitutes in Thailand^{13,14} and prostitutes in certain cities in India.¹⁵

This brief review does not cover in detail the important subjects of HIV transmission in the health care setting and guidelines to prevent such transmission. I do note that health care workers have been reported to seroconvert after exposure to blood from HIV-infected patients. The great majority of such reports are in persons who received parenteral exposures, although the risk after such exposures is low.¹⁶⁻¹⁸ There have also been a few reports of health care workers infected after contact of blood with open wounds, skin with breaks in it (for example, due to dermatitis or chapping), or mucous membranes.¹⁹ A recent report described HIV infection in five patients without established risk factors who had procedures performed by an HIV-infected dentist who did not always follow recognized infection control guidelines.^{20,21} DNA sequence analysis showed that the HIV strains from these patients were similar (although not identical) to each other and those of the dentist. The exposure that may have resulted in viral transmission to these patients could not be conclusively identified, and the precise mode of HIV transmission is uncertain. Other investigations of HIV-infected health care workers (such as surgeons) who performed invasive procedures have not found evidence of HIV transmission to their patients²²; these and other data support the assertion that there is an extremely low risk of a patient acquiring HIV infection during an invasive procedure.²³

In addition to an awareness of how HIV is transmitted, it is equally important to know how HIV is not transmitted. National surveys conducted in 1987 and 1988 showed an increasing proportion of persons saying that it was "very unlikely" or "definitely not possible" to acquire HIV through exposures such as eating in a restaurant where the cook had the AIDS virus, using public toilets, or working near someone with the AIDS virus.²⁴ At least a dozen studies have evaluated over 800 household or boarding school contacts of persons with AIDS or HIV infection and have not found evidence of transmission through such exposures.^{25,26} For example, one study evaluated 206 household contacts of 90 persons with AIDS.²⁷ These contacts did not have additional risk factors for HIV infection; for example, they were not sexual partners of the HIV-infected persons or infants born to HIV-infected women. Personal contacts with the AIDS patients in some cases included sharing a bath or toilet, sharing household items such as towels and eating utensils, shaking hands, kissing on the cheek, and helping the person

to bathe, dress, or eat. None of the contacts were found to be seropositive for HIV antibody.

Of those children with AIDS, 84% have a mother who is either known to be HIV-positive or to belong to a high-risk group, 5% have hemophilia or other coagulation disorders, 9% have received blood or blood components, and for 2% the risk history is undetermined. An analysis of data for children whose risk history is undetermined also suggests that risk information (particularly concerning the mother) is often incomplete.²⁸ With respect to transmission from a woman to her newborn, infection is generally thought to occur in utero and possibly at the time of delivery; a few reports have also suggested the possibility of transmission through breast-feeding,^{29,30} although the importance of this route of transmission remains to be determined.

Factors Facilitating Sexual Transmission

As previously mentioned, most adults with AIDS are thought to have acquired HIV infection through sexual transmission. Factors possibly facilitating such transmission include specific sexual practices, the clinical and immunologic status of the HIV-infected sexual partner, and the presence of other sexually transmitted diseases.

Among gay and bisexual men, the sexual practice most highly associated with HIV infection is receptive anal intercourse.³¹ Although anal intercourse may also be associated with an increased risk of HIV infection among heterosexual couples, most HIV infection resulting from heterosexual contact has occurred among those who reported only vaginal intercourse.³² Several case reports have also described HIV infection in association with receptive oral intercourse.^{33,34} For example, a recent report described the cases of two men who seroconverted for HIV antibody and who reported no anal intercourse for at least five years preceding the estimated date of seroconversion.³³ Both men reported multiple episodes of receptive oral intercourse with ejaculation. Although other practices (such as unprotected anal intercourse) may be associated with a higher risk of HIV infection, receptive oral intercourse is therefore associated with a potential risk of HIV infection.

Studies have also suggested that sexual transmission is more likely to occur when the HIV-infected partner has clinical or laboratory evidence of immunodeficiency, such as AIDS or a low CD4⁺ lymphocyte count.^{35,36} This may be due to a greater viral burden and a greater number of virus-infected cells in the seropositive partner, increasing the likelihood of HIV transmission to a seronegative partner.

A number of studies have suggested that HIV transmission may be facilitated by the presence of other sexually transmitted diseases associated with genital ulcers, such as herpes, syphilis, or chancroid.³⁷ A possible reason is that genital ulcers may disrupt the skin or mucosal lining, thereby facilitating HIV transmission. Recent studies from Africa have also described nonulcerative sexually transmitted diseases as possibly promoting heterosexual transmission. For example, gonorrhea and chlamydial infection were identified as risk factors for HIV infection among female prostitutes in Zaire.³⁸ Possibly these findings are due to cervicitis, either because of an increased number of target cells or because of cervical changes that increase the likelihood of HIV infection. It is clear that for many reasons, the control of sexually transmitted disease is integrally related to preventing the spread of HIV.

'Natural' History of HIV Infection

Many prospective studies have evaluated the prognosis of HIV infection, including the development of AIDS and other manifestations of HIV disease.³⁹ In one prospective cohort study of homosexual and bisexual men, the San Francisco City Clinic Cohort Study, the date of HIV seroconversion could be reliably determined for a subset of all seropositive men.⁴⁰ Among these men, the likelihood of AIDS developing was low for the first few years after HIV infection, with only 1% of infected men having progression to AIDS within two years of seroconversion.⁴¹ The cumulative risk of AIDS then increased over time, with an estimated 12% of HIV-infected men having AIDS within 5 years, 53% within 10 years, and 61% within 11.8 years after HIV seroconversion (95% confidence interval, 56% to 66%).

Whether other factors besides the duration of HIV infection affect the likelihood of AIDS is an area of active investigation. In the laboratory, several infectious agents, such as certain herpesviruses, have been shown to affect the replication of HIV⁴²; however, the existence of an infectious cofactor increasing the likelihood of progression to AIDS based on in vivo data remains uncertain. Other factors possibly affecting the progression of HIV infection to AIDS include genetic background (such as HLA type),⁴³ age,⁴⁴ characteristics of the viral strain or strains infecting a person (including cellular host range and pathogenicity), immunologic response to HIV infection (including CD8⁺ suppressor cell activity),⁴⁵ and other infectious agents theoretically serving as cofactors. Possibly multiple factors, acting in a complex interrelationship, modulate the likelihood of specific manifestations of HIV disease developing.

A major factor affecting HIV disease progression may be the use of antiviral therapies such as zidovudine (AZT). Placebo-controlled studies have indicated that the use of zidovudine in either asymptomatic⁴⁶ or mildly symptomatic⁴⁷ HIV-infected persons with a CD4⁺ count of less than 500 cells per μ l decreases the rate of progression to AIDS or severe AIDS-related conditions. Based on these data, zidovudine is currently licensed to be given to HIV-infected people with a CD4⁺ count of less than 500 cells per μ l. Given the many who are estimated to be infected with HIV,³ meeting the needs for antiviral and other prophylactic therapies is an important issue for those involved in planning health services and health care delivery.

Predictors of Outcome

One of the most important questions concerning the outcome of HIV infection is identifying those cases that are most likely to progress to AIDS. Studies have identified various signs and symptoms associated with an increased likelihood of progression. These include certain oral manifestations of HIV (such as oral candidiasis), the presence of certain signs and symptoms (such as fever or weight loss), and severe herpes zoster.⁴⁸⁻⁵⁰ Although generalized lymphadenopathy may be associated with HIV infection, among those who are HIV infected, a number of studies have indicated that people with lymphadenopathy are not significantly more likely to have progression to AIDS.^{48,49}

Certain laboratory tests may also help predict in whom AIDS is most likely to develop. One of the most important predictors is the CD4⁺, or T-helper, count. Both the absolute CD4⁺ count and the percentage of CD4⁺ cells have been shown to have prognostic significance.^{44,48,49,51} For example,

in the San Francisco General Hospital Study, of HIV-infected homosexual and bisexual men whose baseline CD4⁺ count was 200 cells per μ l or less, 87% progressed to have AIDS within three years; of those men with a baseline value of over 400 cells per μ l, only 16% had progression to AIDS.⁴⁸ Other studies that looked at specific disease outcomes have shown that persons in whom *P. carinii* pneumonia developed were likely to have low CD4⁺ counts preceding their diagnosis.^{52,53} Based on such data, the Public Health Service currently recommends prophylaxis against *P. carinii* pneumonia for HIV-infected persons with a CD4⁺ count of less than 200 cells per μ l or less than 20% of the total lymphocytes.⁵⁴

Other laboratory measurements besides the CD4⁺ count have been shown to have prognostic importance for HIV disease progression. Two of the most powerful predictors have been p24 antigen and β_2 -microglobulin; for example, studies have shown increased progression for persons with an assay positive for p24 antigen^{44,48} or an elevated β_2 -microglobulin level.^{48,55} Various combinations of the CD4⁺ count, p24 antigen, and β_2 -microglobulin may have even greater predictive value. Studies have also suggested that the serum neopterin level may have prognostic value⁵¹; however, neopterin and β_2 -microglobulin appear to be highly correlated, and the prognostic information from one assay may not be substantially improved by information from the second.

Survival

Of those adults diagnosed with AIDS, 64% are known to have died. Of those diagnosed in 1984 or earlier, however, more than 90% are known to have died¹; additional persons may have died and not been reported to the AIDS surveillance system. Of those children diagnosed with AIDS, 52% are known to have died. For those persons in San Francisco whose AIDS was diagnosed from 1981 through 1989, the estimated median survival was 15.0 months.⁵⁶ The median survival rose, however, from 11.2 months for those diagnosed between 1981 and 1985 to 18.4 months for those diagnosed between 1987 and 1989. Studies in other areas (for example, in Washington State) have also identified increases in median survival.⁵⁷ There are a number of possible reasons for these changes, including an earlier diagnosis of AIDS, the use of antiviral therapies such as zidovudine, and other improvements in medical care.

Kaposi's Sarcoma

Surveillance data suggest that the distribution of AIDS-defining diseases may be different in different risk groups and that patterns of disease may be changing over time. A disease of particular interest is Kaposi's sarcoma. Among adults with AIDS, the proportion of homosexual or bisexual men with Kaposi's sarcoma is much greater than for other persons. In an analysis of US surveillance data for persons with AIDS, the percentage reported to have Kaposi's sarcoma ranged from 21% for homosexual and bisexual men to only 1% for persons with hemophilia; homosexual and bisexual men had a substantially higher risk of Kaposi's sarcoma than did any other transmission group.⁵⁸ In addition, national and San Francisco surveillance data^{59,60} and data from well-characterized cohorts of homosexual and bisexual men⁶¹ indicate a significant decline over time in the proportion of persons with AIDS who present with Kaposi's sarcoma.

Kaposi's sarcoma may differ from other AIDS-related illnesses in several ways. Analysis of data from the San Fran-

cisco City Clinic Cohort Study suggests that Kaposi's sarcoma may have a shorter incubation time (from HIV infection to diagnosis) and longer survival time (from diagnosis to death) than other AIDS-defining diseases.^{61,62} This is consistent with other data indicating that AIDS patients with opportunistic infections tend to have lower CD4⁺ counts than persons with Kaposi's sarcoma alone⁶³ and suggests that this disorder develops at an earlier stage of immune suppression than certain other AIDS-defining diseases.

Several studies have suggested that Kaposi's sarcoma may be associated with a cofactor that increases the likelihood of its development. An analysis of national surveillance data suggested that such a cofactor may be sexually transmitted.⁵⁸ If so, identifying such an agent will be important for helping to understand more about the pathogenesis of Kaposi's sarcoma and may have implications for both the prevention and treatment of this AIDS-related illness.

Conclusion

In this brief review I have addressed only some of the many important issues and unresolved questions concerning the epidemiology of AIDS and HIV infection. The acquired immunodeficiency syndrome continues to provide challenges to health care professionals in many areas. One such challenge is for health care professionals to serve as educators concerning the epidemiology of AIDS, including the ways HIV is and is not transmitted. By doing so, they assist not only patients and their families but members of the community who look to them for guidance.

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